

Anaphylaxis from ingestion of mites: Pancake anaphylaxis

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Oral mite anaphylaxis is a new syndrome characterized by severe allergic symptoms occurring immediately after eating foods made with mite-contaminated wheat flour. This syndrome, which is more prevalent in tropical environments, is triggered more often by pancakes, and for that reason, it has been designated “the pancake syndrome.” Because cooked foods are able to induce the symptoms, it has been suggested that thermoresistant allergens are involved in its pathogenesis. A variety of this syndrome can occur during physical exercise (dust mite ingestion–associated exercise-induced anaphylaxis). (J Allergy Clin Immunol 2013;131:31-5.)

Key words: Anaphylaxis, exercise-induced anaphylaxis, food allergy, IgE, mites

In our new mini-series, “Allergy and clinical immunology around the world,” we ask experts from different parts of the world to tell us about issues that are of particular interest in their regions, reflecting either distinctive diseases or unique approaches to common problems.

Domestic mites have been recognized as the most important allergenic source responsible for highly prevalent allergic diseases, such as asthma, rhinitis, and atopic dermatitis.¹ Since 1982, our group observed a number of atopic patients with severe allergic symptoms immediately after eating foods prepared with wheat flour contaminated with mites. This new syndrome has been designated oral mite anaphylaxis (OMA) or “pancake syndrome.” In this article we summarize the clinical and experimental observations on this allergic disorder that have been published since 1993. Interestingly, in 1963, Herranz² reported the case of a 56-year-old man who died after a massive ingestion of mites contained in a pap (soft semiliquid food, usually mashed or pulped, especially for babies or sick people) made with milk and wheat flour. Autopsy revealed intense bowel irritation and disseminated granulomas in multiple organs, and *Tyroglyphus farinae* mites were present in stools and the gut.

Although most cases of OMA have been reported from countries located in tropical areas of the world, new patients

Abbreviations used

NSAID: Nonsteroidal anti-inflammatory drug

OMA: Oral mite anaphylaxis

from more temperate regions are being increasingly observed, especially in North America (see below). Because most patients with OMA might not be properly managed, clinicians around the world should be aware of this clinical picture and be ready to recognize, treat, and prevent the occurrence of this life-threatening condition. Further investigations on this syndrome could provide new research directions for a better understanding of the basic mechanisms of allergic inflammation and hopefully for new therapeutic strategies for allergic diseases.

OMA

Various contaminants with pathogenic potential are often present in food. Among them, the most frequent are microorganisms (bacteria, viruses, and parasites), toxins, chemical substances, food additives (dyes, sulfites, and benzoic acid), allergens from other foods, cross-reacting allergens from pollens and latex, and drugs (penicillin).

In 1995, the first 2 cases of systemic reactions induced by the ingestion of beignets contaminated with mites were reported in Detroit and Philadelphia. These 2 patients ingested beignets prepared with a beignet mix mailed from New Orleans.^{3,4} After those initial cases, a number of patients with this clinical picture have been described in different parts of the world, including North America, South America, Asia, and Europe (Table 1³⁻²⁰). In addition to the list of cases included in Table 1, we are aware of unpublished cases in other locations, including the Dominican Republic, Peru, Colombia, Israel, and New Zealand. Only 2 small series of patients from Caracas, Venezuela, and the Canary Islands, Spain, have been reported.^{7,8}

In general, most cases have been observed in tropical and subtropical locations in which climatic conditions, especially high temperature and relative humidity, are favorable for mite proliferation in the food. Outside the intertropical region, there are only 2 cases, one in Porto Alegre, Brazil, and one in Massachusetts in the United States (Fig 1).^{9,13} Sometimes the contaminated flour has been transported from distant locations (eg, patients with OMA seen in Detroit or Philadelphia). This syndrome frequently goes unnoticed or is wrongly confused with allergy to wheat, and quite often, allergologic evaluation is not requested.

Most publications are on isolated case reports and small series of patients. Major differences between the reports in the literature are related to the number of patients studied, geographic setting, and mite species involved. The clinical picture and induction by mite-contaminated food prepared with wheat flour are common to

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TABLE I. Published cases of OMA until May 31, 2012 (n = 135)

Author (year)	No.	Age (y)	Sex (M/F)	Location	Foods	Mites	NSAID hypersensitivity
Erben et al (1993) ³	1	48	1/0	Detroit (United States)	Beignets	<i>Dermatophagoides farinae</i>	No
Spiegel et al (1994) ⁴	1	17	0/1	Philadelphia (United States)	Beignets	<i>Dermatophagoides farinae</i>	No
Skoda-Smith et al (1996) ⁵	1	14	1/0	Birmingham (United States)	Pizza dough	<i>Dermatophagoides farinae</i>	Family history
Matsumoto et al (1996) ⁶	2	11, 14	1/1	Kumamoto (Japan)	“Okonomi-yaki”	<i>Tyrophagus putrescentiae</i>	No
Blanco et al (1997) ⁷	16	13-38	4/12	Canary Islands (Spain)	Various	<i>Dermatophagoides farinae</i> <i>Tyrophagus entomophagus</i>	14 (87%)
Sánchez-Borges et al (1997) ⁸	31	13-45	14/17	Caracas (Venezuela)	Various	<i>Dermatophagoides farinae</i> <i>Suidasia</i> species <i>Aleuroglyphus ovatus</i>	20 (66%)
Guerra-Bernd et al (2001) ⁹	1	18	0/1	Porto Alegre (Brazil)	Polenta	<i>Tyrophagus</i> species <i>Dermatophagoides farinae</i> <i>Dermatophagoides pteronyssinus</i>	Yes
DeMerrell et al (2004) ¹⁰	1	11	1/0	New Orleans (United States)	Beignets	<i>Dermatophagoides pteronyssinus</i>	No
Ott (2004) ¹¹	1	54	0/1	Minnesota (United States)	Pancakes	<i>Dermatophagoides pteronyssinus</i> (?)	No
Wen et al (2005) ¹²	1	8	1/0	Taipei (Taiwan)	Pancakes	<i>Blomia freemani</i>	No
Miller and Hannaway (2007) ¹³	1	52	0/1	Massachusetts (United States)	Pancakes	<i>Dermatophagoides farinae</i>	No
Tay et al (2008) ¹⁴	2	15, 30	0/2	Singapore	Wheat flour-coated fish, scones	<i>Dermatophagoides farinae</i>	Yes
Iglesias-Souto et al (2009) ¹⁵	1	13	1/0	Canary Islands (Spain)	Pancake	<i>Tyrophagus entomophagus</i>	Yes
Geller (2009) ¹⁶	1	36	0/1	Rio de Janeiro (Brazil)	Pancake	<i>Aleuroglyphus ovatus</i>	Yes
Sánchez-Machín et al (2010) ¹⁷	42	11-57	21/21	Canary Islands (Spain)	Pancakes	<i>Tyrophagus entomophagus</i>	21 (50%)
Barrera et al (2011) ¹⁸	1	22	1/0	Panama	Pancakes	<i>Blomia tropicalis</i> <i>Dermatophagoides pteronyssinus</i>	No
Takahashi et al (2011) ¹⁹	30	NA	NA	Japan	“Okonomi-yaki” “Takoyaki”	<i>Tyrophagus putrescentiae</i> <i>Dermatophagoides pteronyssinus</i> <i>Dermatophagoides farinae</i>	No
Posthumus and Borish (2012) ²⁰	1	71	1/0	Charlottesville (United States)	Grits	<i>Dermatophagoides farinae</i>	No

Modified with permission from Sánchez-Borges et al.²⁷ Fifty-nine (43.7%) of 135 subjects had hypersensitivity to NSAIDs.

F, Female; M, male; NA, not available.

all the reports (Table I). Contamination of wheat flour with mites can occur in locations other than the tropics. Also, a patient with OMA after eating grits contaminated with *Dermatophagoides farinae* (purchased in South Carolina) was reported recently from Charlottesville, Virginia.²⁰

CLINICAL PICTURE

The clinical data in our first 30 patients with OMA are summarized in Table II. Most patients are adolescents and young adults, and there is no predominance of sex. All of them have a previous history of atopic disease, more often rhinitis, asthma, or both. Symptoms typically begin within the first 10 to 45 minutes after the meal, but in 1 patient they occurred after 240 minutes. Pancake syndrome also occurs in children.²¹

Outstanding symptoms are dyspnea, face and laryngeal angioedema, wheezing, and other upper and lower airway manifestations. Acute respiratory failure, requiring transfer to the intensive care unit and intubation, has occurred in some patients (≥ 4 in our centers). Two deaths associated with the ingestion of foods contaminated with mites have been reported in the literature.^{22,23} We also described the case of a 16-year-old girl with OMA

while playing soccer after eating pancakes contaminated with the mite *Suidasia medanensis*. This clinical pattern has been designated dust mite ingestion-associated exercise-induced anaphylaxis.²⁴

CAUSE AND PATHOGENESIS

Foods prepared with wheat flour, most commonly pancakes, are involved in the induction of OMA (Table II). In the literature there are reports of OMA associated with beignets and “okonomi-yaki” (bonito and mackerel covered with flour). The species name *D farinae* originates from the observation that this mite was found in flour (“farina” in Latin). Other foods that more likely can be contaminated with mites are cheese, ham, chorizo, and salami. Because the clinical picture appears after consuming heat-treated meals, skin tests were performed with unheated and heated mite-contaminated flour extracts in subjects with mite allergy. After heating, skin prick testing with the flour extract resulted in a reduced but persistently positive wheal-and-flare response. These results suggest that mite group 2 (thermorestable allergens) is probably involved in the production of OMA because group 1 allergens are heat labile.²⁵ In agreement with this hypothesis, we did not find Der p 1 or



FIG 1. World map showing the number of cases of OMA in different countries: Spain (n = 59), Japan (n = 32), Venezuela (n = 31), United States (n = 7), Brazil (n = 2), Taiwan (n = 1), Singapore (n = 1), and Panama (n = 1).

Der f 1 allergens in wheat flour samples obtained from patients with OMA,⁸ whereas Blanco et al⁷ detected significant quantities of group 2 but limited amounts of group 1 dust mite allergens in contaminated flour. This hypothesis has been confirmed in a recent report.²⁰

Mites responsible for OMA include domestic species (*Dermaphagoides pteronyssinus*, *D farinae*, and *Blomia tropicalis*), as well as storage mites (*S medianensis*, *Aleuroglyphus ovatus*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, *Tyrophagus entomophagus*, and *Blomia freemani*).

A possible increased prevalence of cutaneous hypersensitivity (urticaria and angioedema) induced by nonsteroidal anti-inflammatory drugs (NSAIDs) has been reported in patients with OMA.²⁶ Because of this association, “a new aspirin triad” was proposed. This potential clinical triad is characterized by allergic rhinitis, aspirin hypersensitivity, and severe reactions to the ingestion of mite-contaminated foods.²⁷ The reasons for this association have not been elucidated because mite-induced anaphylaxis is mediated by mite-specific IgE, whereas most reactions to NSAIDs occur in patients affected by inhibition of COX-1 and are not dependent on IgE. The possible mechanisms that could explain this association have been recently reviewed and include the inhibition of COX-1 by mite constituents; predisposing genetic factors, such as polymorphisms of leukotriene C₄ synthase; stimulation of innate immunity by mite products; protease activity; Toll-like receptor 4-mediated inflammation; and epigenetic modifications.²⁶

RISK FACTORS

The following risk factors for the development of OMA have been identified:

1. previous atopic disease;
2. mite sensitization;
3. NSAID hypersensitivity;

4. ingestion of pancakes or other meals containing wheat flour; and
5. ingestion of more than 1 mg of mite allergen (>500 mites per gram of flour).

The fact that only a subset of atopic patients will have OMA is intriguing and has led investigators to consider other possible underlying factors predisposing these subjects to react acutely to mite-contaminated foods. Presently, there is no evidence supporting any of the other susceptibility factors for anaphylaxis, such as mast cell activation syndrome, increased oral/gastrointestinal mucosal permeability, or pre-existing mite-specific IgE levels.

DIAGNOSIS

This clinical condition should be suspected in patients with acute symptoms during or immediately after eating foods prepared with wheat flour. Physicians working in emergency departments are advised to consider OMA in patients presenting with acute angioedema or laryngeal edema associated with the ingestion of pancakes, particularly if the event occurred in or the flour originated from tropical or subtropical climates. In regard to the possible induction of symptoms through mite contamination of other grains, in our experience only 1 patient showed OMA after the ingestion of a cornmeal cake made with a commercial mix containing corn and wheat flour. However, the possibility of mite contamination of other flours or grain products needs to be considered.

OMA can be confirmed in patients who meet the following criteria:

1. compatible symptoms occurring after eating foods prepared with wheat flour;
2. previous history of rhinitis, asthma, atopic eczema, or food allergy;

TABLE II. Clinical data in 30 patients with OMA

	No.
Sex	
Female	16
Male	14
Mean age (y [range])	21.1 (13-45)
Time of the reaction after food intake (min [range])	43.9 (10-240)
Allergic history	
Asthma + rhinitis	14
Rhinitis	12
Asthma	1
Asthma + rhinitis + atopic dermatitis	1
Rhinitis + atopic dermatitis	1
Rhinitis + conjunctivitis	1
Foods*	
Pancakes	16
Sponge cake	5
Pizza	2
Pasta	2
Steak parmigiana	2
Corn cake (mixed corn and wheat flour)	2
Wheat bread	2
Tequeños (wheat flour and cheese appetizer)	1
Alfajor (wheat and milk sweet)	
White sauce	1
Symptoms	
Breathlessness	27
Angioedema	15
Wheezing	12
Rhinorrhea	9
Cough	8
Stridor	6
Dysphagia	6
Urticaria	6
Abdominal cramps	4
Conjunctivitis	3
Skin rash	2
Dysphonia	2
Sneezing	1
Vomiting	1
Cyanosis	1
Pruritus	1
Tachycardia	1

*Three patients reacted to 2 mite-contaminated foods.

- demonstration of mite-specific IgE *in vivo* (immediate-type skin tests) or *in vitro*;
- positive skin test response induced by an extract of the incriminated flour;
- negative skin test response to commercial wheat extract and to an extract of uncontaminated flour;
- tolerance to other foods made with uncontaminated wheat flour;
- microscopic identification of mites in the suspected flour;
- presence of mite allergens in the flour, as demonstrated by means of immunoassay; and
- aspirin/NSAID hypersensitivity.

PROPHYLAXIS

Low temperatures prevent the proliferation of mites in the flour, and in especially warm climates, it is likely that storing the flour in sealed plastic or glass containers in the refrigerator will prevent

OMA. Other hygienic environmental measures to be implemented in the homes of patients with OMA include improved air quality through air purifiers, measures to decrease intradomiciliary humidity, cleaning and disinfection of furniture and floors, and use of acaricides.

UNMET NEEDS

The following issues require further study:

- variability with only selected allergic patients experiencing OMA;
- role of genetic factors;
- pathogenetic mechanisms to explain the apparent rapid absorption of mite allergens across the gastrointestinal mucosa;
- effects of childhood oral exposures to mite allergen in the induction of sensitization or tolerance;
- efficacy of oral or sublingual immunotherapy;
- characterization of the responsible allergens;
- importance of cross-reactions among allergens from different mite species, such as sensitization to house dust mites resulting in symptoms from ingestion of flour contaminated with storage mites; and
- verification of the potential relationship between OMA and NSAID hypersensitivity.

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